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(54) Title: TASTE MASKING OF IBUPROFEN BY FLUID BED COATING

(57) Abstract

A chewable taste-masked ibuprofen tablet having controlled release characteristics.

Chewable
Not quick dissolve

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TASTE MASKING OF IBUPROFEN BY-FLUID BED COATING

BACKGROUND OF THE INVENTION

Ibuprofen is a well-known therapeutic agent. Its therapeutic activities include analgesia and anti-pyretic attack. As with most medicines, one of the difficulties with ibuprofen is in making it palatable to children. This difficulty has been overcome with most medicines by preparing formulations such as syrups and drops. The present invention relates to chewable tablets that are palatable to children and a process for making the tablets.

From a manufacturing cost standpoint, it is desirable to have chewable, taste-masked microcapsules that are large (0.25-1 mm in diameter), because larger microcapsules are easier to manufacture and package, and are less expensive to produce than are small microcapsules. However, an increase in size makes fracture during chewing and the release of drug from the microcapsule more likely to occur especially when there is an inadequate amount of plasticizer or other component included to provide elasticity. A larger sized microcapsule requires greater elasticity to minimize the likelihood that a fracture will occur and active agent will be released. There is therefore a need in the art of pharmaceutical formulation to provide encapsulating coatings capable of being formulated into chewable microcapsules as large as about 1.5 mm. that will not release drugs during chewing.

INFORMATION DISCLOSURE

Ibuprofen and its use for treatment of analgesia is disclosed in U.S. patent 3,385,886. Compositions containing ibuprofen and methods for using them are described in U.S. patent 3,228,831. New crystalline and high dose formulations of ibuprofen are disclosed in U.S. patents 4,476,248 and 4,609,675 respectively.

Microencapsulation is described by J.A. Bakan, Part Three of "The Theory and Practice of Industrial Pharmacy", 1986, pp. 413-429.

EUDRAGIT L30D is a known polymer useful for coating orally administered pharmaceutical dosage forms, particularly tablets, capsules and pills, with coatings which are resistant to gastric juices but solvent in intestinal juices.

Chewable taste-masked pharmaceutical compositions, including some containing ibuprofen, are described in U.S. patent 4,800,087. However, the compositions described therein require a coating consisting of a mixture of polymers. The use of fluidized bed for coating pharmaceutical products is described in U.S. Patent 4,800,087.

SUMMARY OF THE INVENTION

This invention involves:

A chewable taste-masked tablet having controlled release characteristics comprising a microcapsule of about 100 microns to about 0.8 mm in diameter having (a) a pharmaceutical core including crystalline ibuprofen and (b) a methacrylic acid copolymer coating having sufficient elasticity to withstand chewing.

While chewable taste masked formulations of ibuprofen are referred to in the prior art, among the advantages of the compositions of this invention over the closest prior art compositions is that the coating used consists of a single copolymer rather than a mixture of copolymers.

DETAILED DESCRIPTION OF THE INVENTION

The present invention comprises formulations of taste-masked microcapsules which further comprise (a) a pharmaceutical core of crystalline ibuprofen and (b) a methacrylic acid copolymer coating that may provide chewable taste-masked characteristics. Both the polymeric coating and the pharmaceutical core may further comprise diluents, fillers and other pharmaceutical additives which may effect the rate of release of active ibuprofen from the microcapsule.

The methacrylic acid copolymer is preferably dispersable in water so as to take advantage of aqueous formulation techniques and has a rapid rate of dissolution at a pH of about 5.5.. Aqueous-based coating systems are safe and make regulatory compliance (EPA) relatively easy compared to non-aquaous based coating systems. An elastic microcapsule which will not release ibuprofen in the mouth when chewed is contemplated by the present invention.

A preferred coating composition is a high temperature film forming polymer or "hard" polymer. A hard polymer is defined as a polymer that will form a film on a pharmaceutical core at a temperature of at least about 30°C. Examples of high temperature film forming polymers useful in this invention include hydroxypropylmethyl cellulose, for example, Pharmacoat' 606 brand from Shinetro Corp., Tokyo, Japan, hydroxypropyl cellulose, for example, Klucel' brand from Hercules Corp., Wilmington, Del., methylcellulose for example Methocel A', from Dow Chemical, Midland, Mich., ethylcellulose, for example, Ethocel' brand from Dow Chemical Corp., and other aqueous polymeric dispersions such as Aquacost' Brand from FMC, Philadelphia, PA., and Surelease' brand from Colorcon, West Point, PA., polyvinyl alcohol, polyvinyl

acetate, cellulose acetate butyrate, styrene acylate copolymers, for example Janocryl 138 (61°C. film forming copolymer from S.C. Johnson, Racine, Wis.) and copolymers of acrylic acid esters, for example, the EUDRAGIT Copolymers (Rohm Pharma GmbH Westerstadt, W. Germany): Eudragit' L30D, Eudragit' L100-55, Eudragit' RS(30D and 100).

Eudragit' copolymers that are preferred in embodiments of this invention include L30D, an anionic copolymer based of polymethacrylic and acrylic acid esters (Methacrylic Acid Copolymer, Type C in USP XXL/NF XVI) with a mean molecular weight of 250,000.

The polymeric coating should provide for immediate release characteristics, i.e., rapid release of the active agents in the duodenum within a period of about one hour. When the microcapsules are formulated into chewable, taste-masked oral tablets or capsules, the formulations provide for immediate, rapid release in the stomach.

The chewable polymeric coating providing immediate release upon reaching the duodenum i.e., within one hour after ingestion may be comprised of a pharmaceutically compatible high temperature film forming polymer that is water insoluble or not swellable within the pH range (about 5.5-6.5) and/or the liquid content of the mouth and will not release the active agent in the mouth, but will dissolve or change in physical character in the duodenum, for example, swell or become more porous, thus releasing drug.

The most preferred film forming acrylic resin polymer that releases active agent rapidly in duodenum is EUDRAGIT L30D. EUDRAGIT L30D is a copolymer anionic in character, based on polymethacrylic acid and acrylic acid esters. Although EUDRAGIT L30D is soluble at pH's in the mouth and insoluble at pH's of the stomach, it has found usefulness in chewable, taste-masked immediate release formulations of the present invention. This usefulness may stem from the lack of liquid in the mouth, or may be the result of elastic qualities that EUDRAGIT L30D acquires when formulated in combination with a plasticizer, or preferably, with EUDRAGIT E30D.

Any of the above described high-temperature film-forming polymers may be used for microencapsulation. However, to make capsules of the required elasticity using the above described high temperature film forming polymers, plasticizers may be incorporated into the coatings. Plasticizers useful to provide the requisite elasticity include propylene glycol and polyalkylene glycols, for example, polyethylene glycol,

triacetin, (glyceryl triacetate from Eastman Kodak, Rochester, NY vinyl pyrrolidone, diethyl phthallate, dibutylsebacate, and esters of citric acid among others. Generally, the plasticizers comprise between about 2% and about 50% by weight of polymer and plasticizer combined, preferably between about 5% and 15% by weight and most preferably about 10% by weight of the polymer and plasticizer combined.

The chewable tablets of this invention are prepared by spraying a solution of the methacrylic acid copolymer on to a fluidized bed of crystalline ibuprofen.

Crystalline ibuprofen can be prepared by the process described in U.S. Patent 4,476,248. The particle size of the ibuprofen should be about 80 to 500 microns and it it may contain excipients such as starch, lactose, hydroxypropyl methylcellulose, microcrystalline cellulose PVP, sucrose and fructose.

The residence time should be such that the ratio of copolymer to ibuprofen of each chewable tablet is about eight percent by weight.

The temperature of the inlet and outlet air should be maintained between 40 and 60 C. 20 and 40 C. respectively. The preferred inlet and outlet air temperatures are between 45 and 55 and 33 and 27°C respectively.

The temperature of the fluidized bed should be maintained between 60 and 20, respectively. The preferred temperature of the bed is about 35 C.

The amount of ENDRAGIT L30D in the encapsulation formulation should be between about 10% to 60% by weight of ibuprofen, preferably about 14%.

EMBODIMENT OF THE INVENTION

Example 1 Preparation of chewable ibuprofen tablet (#13, p 23)

A. Encapsulated Ibuprofen

Ibuprofen	4 Kg
Eudragit L30D	2.33 Kg (coating polymer)
Propylene Glycol	140 gm (plasticizer)
Talc	200 gm
Purified Water	200 gm

Ibuprofen crystals (particle size #40-105) are air suspended in a closed chamber (Glatt GPCG5). An aqueous dispersion of Eudragit L 30D and talc is sprayed onto the fluidized bed of ibuprofen at a rate of 60gm/min. The inlet and outlet air temperature are maintained at 50°C. and 20-22°C. respectively. The air rate is adjusted so as to maintain the particles in a suspended state and to maintain the fluidized bed at a temperature of 35°C.

Air Atomizing Pressure 3.5 bar

B. Preparation of Chewable Tablets

	Per Tab	Per 1000 Tab
Mannitol	5-44 mg	544 Gm
Malic Acid	4 mg	4 Gm
Aspartame	12 mg	12 Gm
Spray Dried Orange Flavor	18 mg	18 Gm
Encapsulated Ibuprofen	127 mg	127 Gm
Ac-Di-Sol	24 mg	24 Gm
Avicel pH102	60 mg	60 Gm
F.D.C. Yellow 6 Lake	0.2 mg	0.2 Gm
Citric Acid	4 mg	4 Gm
Talc	20 mg	20 Gm

The compression mix of above was tabletted on a Manesty beta press with 1/2" flat face tooling. Tablet weight: 813 mg. Hardness: 9 - 13 Strong Cobert (SC). Disintegration Time in water: 2 minutes.

Table 1 shows a comparison of dissolution data between MOTRIN IB Tablet in PH 7.2 and the MOTRIN Chewable Tablets of this invention.

Table 2 shows a comparison of dissolution data between MOTRIN IB Tablets in PH 5.8 and the MOTRIN Chewable Tablets of this invention.

TABLE I

Comparison of Dissolution Data between Motrin IB and Motrin Chewable Tablets

Buffer 7.2 PH

Motrin IB		#12		#13		Recrystallized Ibuprofen Raw Material	
Flask 1		Flask 2		Flask 3		Flask 4	
Time	% Released	Time	% Released	Time	% Released	Time	% Released
0.10	-0.02	0.20	0.00	0.30	0.04	0.40	-0.02
2.10	1.21	2.20	10.50	2.30	9.40	2.40	0.48
4.10	38.77	4.20	63.24	4.30	53.61	4.40	18.34
6.10	71.49	6.20	89.31	6.30	84.02	6.40	40.63
8.10	84.88	8.20	97.65	8.30	89.89	8.40	54.00
10.10	90.60	10.20	95.85	10.30	90.91	10.40	63.24
12.10	92.79	12.20	93.61	12.30	91.45	12.40	71.12
14.10	93.80	14.20	91.77	14.30	91.45	14.40	78.23
16.10	94.36	16.20	91.38	16.30	91.62	16.40	85.25
18.10	94.58	18.20	91.64	18.30	91.66	18.40	87.75
20.10	94.67	20.20	91.86	20.30	91.68	20.40	94.43
22.10	94.75	22.20	91.88	22.30	91.77	22.40	96.05
24.10	94.77	24.20	92.01	24.30	91.79	24.40	99.24
26.10	94.82	26.20	92.16	26.30	91.77	26.40	100.63
28.10	94.88	28.20	92.40	28.30	91.79	28.40	101.32
30.10	94.92	30.20	92.57	30.30	91.81	30.40	101.58
32.10	94.95	32.20	92.79	32.30	91.88	32.40	101.71
34.10	95.01	34.20	92.83	34.30	91.90	34.40	102.14
36.10	94.99	36.20	92.92	36.30	91.86	36.40	102.20
38.10	95.03	38.20	92.96	38.30	91.86	38.40	102.35
40.10	94.99	40.20	93.00	40.30	91.84	40.40	102.46
42.10	95.05	42.20	93.09	42.30	91.90	42.40	102.61
44.10	95.10	44.20	93.15	44.30	91.92	44.40	102.66
46.10	95.08	46.20	93.20	46.30	91.97	46.40	102.72
48.10	95.10	48.20	93.24	48.30	91.97	48.40	102.74
50.10	95.08	50.20	93.26	50.30	91.94	50.40	102.76
52.10	95.14	52.20	93.26	52.30	91.94	52.40	102.79
54.10	95.12	54.20	93.33	54.30	92.01	54.40	102.79
56.10	95.14	56.20	93.35	56.30	92.03	56.40	102.89
58.10	95.18	58.20	93.37	58.30	92.05	58.40	102.85
60.10	95.18	60.20	93.41	60.30	92.05	60.40	102.92

In PH7.2 buffer: Formula #12 shows fustic reline than Motrin IB.
Formula #12, #13 and Motrin IB shows the same reline forte after 10 minutes.

Formula #12, #13 all pass U.S.P. Tablets specification 20 minutes 785%.

Flask 1: Motrin IB.
Flask 2: Motrin chewable experiment Lot 12.
Flask 3: Motrin chewable experiment Lot 13.
Flask 4: Recrystallized Ibuprofen.

TABLE II

Buffer: 5-8 PH

Motrin IB	#12	#13	Recrystallized Ibuprofen Raw Material

Flask 1		Flask 2		Flask 3		Flask 4	
Time	% Released	Time	% Released	Time	% Released	Time	% Released
0.10	0.04	0.20	0.02	0.30	0.00	0.40	0.04
2.10	0.13	2.20	2.76	2.30	2.20	2.40	0.78
4.10	2.25	4.20	9.78	4.30	7.90	4.40	9.18
6.10	19.40	6.20	18.68	6.30	15.72	6.40	36.26
8.10	36.48	8.20	28.10	8.30	25.33	8.40	53.71
10.10	48.08	10.20	36.05	10.30	34.69	10.40	65.90
12.10	57.28	12.20	43.30	12.30	47.11	12.40	75.08
14.10	64.34	14.20	51.49	14.30	56.54	14.40	82.38
16.10	70.09	16.20	58.83	16.30	64.02	16.40	87.39
18.10	74.82	18.20	65.33	18.30	69.91	18.40	91.40
20.10	78.57	20.20	71.02	20.30	74.86	20.40	94.41
22.10	81.73	22.20	76.16	22.30	78.53	22.40	96.78
24.10	84.47	24.20	80.43	24.30	81.51	24.40	98.47
26.10	86.74	26.20	84.02	26.30	83.89	26.40	99.72
28.10	88.68	28.20	86.80	28.30	86.11	28.40	100.65
30.10	90.24	30.20	89.05	30.30	87.78	30.40	101.51
32.10	91.56	32.20	90.99	32.30	89.09	32.40	102.03
34.10	92.70	34.20	92.53	34.30	90.06	34.40	102.53
36.10	93.59	36.20	93.78	36.30	90.95	36.40	103.09
38.10	94.43	38.20	94.79	38.30	91.73	38.40	103.52
40.10	95.21	40.20	95.62	40.30	92.46	40.40	103.91
42.10	95.75	42.20	96.26	42.30	93.00	42.40	104.34
44.10	96.29	44.20	96.76	44.30	93.50	44.40	104.67
46.10	96.67	46.20	97.17	46.30	93.84	46.40	105.08
48.10	96.95	48.20	97.45	48.30	94.15	48.40	105.25
50.10	97.21	50.20	97.65	50.30	94.36	50.40	105.46
52.10	97.54	52.20	97.88	52.30	94.60	52.40	105.72
54.10	97.75	54.20	98.12	54.30	94.77	54.40	105.94
56.10	97.97	56.20	98.25	56.30	94.97	56.40	106.11
58.10	98.12	58.20	98.38	58.30	95.08	58.40	106.29
60.10	98.27	60.20	98.47	60.30	95.18	60.40	106.37

PH 5-8:

After 10 minutes about 10-12% difference action compare #12, #13 with Motrin IB.
After 20 minutes about 7-8% difference when compared #12, and #13 with Motrin IB.
After 30 minutes shows no significant difference among them.

Flask 1: Motrin IB.
Flask 2: Motrin chewable experiment Lot 12.
Flask 3: Motrin chewable experiment Lot 13.
Flask 4: Recrystallized Ibuprofen.

5

CLAIMS

1. A chewable taste-masked tablet having controlled release characteristics comprising a microcapsule of about 100 microns to about 0.8 mm in diameter having (a) a pharmaceutical core including crystalline ibuprofen and (b) a methacrylic acid copolymer coating having sufficient elasticity to withstand chewing.

2. A chewable taste-masked pharmaceutical composition according to claim 1 wherein the copolymer is Eudragit L30D said coating being adapted to release said ibuprofen in the duodenum.

3. The composition according to claim 1, wherein said copolymer coating further comprises a plasticizer.

4. The composition according to claim 2, wherein said copolymer coating further comprises a plasticizer.

5. The composition according to claim 4, wherein said plasticizer is selected from the group consisting of glyceryl triacetate, triethyl citrate, acetyl triethyl citrate, dibutyl sebcate, acetyl tributyl citrate, diethyl phthlate, dibutyl phthlate, glycerine, propylene glycol and polyethylene glycol.

6. The composition according to claim 5 wherein said plasticizer is propylene glycol.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/01089

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: A 61 K 9/20, 9/50, 9/52, 31/19

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	EP, A, 0212751 (FORMENTI) 4 March 1987 see claims 1-5,9,11,13,14,21,22; column 4, lines 33-47; column 5, lines 19-21 and 31; column 9, lines 1-6 --	1-6
Y	EP, A, 0212747 (PROCTER & GAMBLE) 4 March 1987 see claims 1-3,6,7; page 5, lines 24-29 and 35; page 6, lines 1 and 16,17; page 8, lines 28-29 --	1-6
Y	US, A, 4835186 (AMERICAN HOME) 30 May 1989 see claims 1,2,5; column 2, lines 31-33 and 40	1-6

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* Special categories of cited documents: [10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
22nd May 1991	11. 07. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	F.W. HECK

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9101089 SA 44948

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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US-A- 4835186	30-05-89	None	

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